Buprenorphine HCl Buccal Film (BELBUCA), C-III
Abbreviated National Drug Monograph
August, 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]

Description/Mechanism of Action	• Buccal buprenorphine (BBUP) utilizes a mucoadhesive film to deliver buprenorphine via the inner lining of the cheek; it is administered twice-daily for the management of chronic pain. • Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor; analgesia is believed to result from buprenorphine binding with high-affinity to opioid receptors on neurons in the brain and spinal cord.
Indication(s) Under Review in This Document	**FDA-approved indication**: • Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. **Potential Off-label Uses**: • Treatment of acute dental pain **Not indicated for management of opioid use disorder / opioid addiction**
Dosage Form(s) Under Review	75mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg and 900 mcg buccal film
REMS	☒ REMS ☐ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Category C

Executive Summary[1-4]

Efficacy	• Two randomized, placebo-controlled trials document the 12 week analgesic efficacy of twice-daily BBUP in the relief of moderate to severe chronic low back pain in opioid naïve and opioid experienced patients. • There is an additional RCT indicating that patients with chronic pain may be converted, without taper, but with comparable safety and efficacy, from long term morphine or oxycodone (80 to 160 MEDD) to an estimated 50% MEDD dose of BBUP.
Safety	• The most common adverse events associated with BBUP are those known to occur with the use of opioid analgesics. • Buprenorphine produces μ-opioid receptor-mediated but ceiling-limited respiratory depression; abuse or misuse of BBUP may pose an increased risk of overdose and death. Benzodiazepines and other CNS depressants (including alcohol, sedative/hypnotics, neuroleptics, and other opioids) can alter the usual ceiling effect of buprenorphine-induced respiratory depression and magnify other CNS-mediated effects. • QT prolongation has been reported with recommended doses of BBUP; the approved label sets a maximum dose of 900 mcg every 12 hours due to the potential for this adverse effect. • Buprenorphine undergoes extensive metabolism through the CYP3A4 system requiring attention to the potential for significant drug interactions with other

	medications that are substrates, inhibitors, or inducers of this system. • Potential safety advantages of BBUP are the lower risk of respiratory depression due to a ceiling effect on respiratory depression (in the absence of other central nervous system depressants) and lower potential for physical dependence, and lower potential for abuse / addiction than with Schedule II opioids. • The dose of BBUP does not need to be adjusted in patients with renal impairment.
Other Considerations	• In opioid naïve patients BBUP should be initiated at 75 mcg once or twice daily • There us a potential for BBUP to precipitate withdrawal in patients already on opioids; to avoid withdrawal, tapering to < 30 mg morphine equivalent daily dose (MEDD) of the other opioid is recommended before initiating therapy with BBUP. Initial dose of BBUP is then based upon prior daily opioid dose before taper to 30 mg MEDD • Following initial dosing, whether previously opioid-naïve or opioid-experienced, BBUP dose titration can proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days
Projected Place in Therapy	• BBUP may be a consideration in the management of moderate to severe chronic pain that requires round-the-clock long term opioid therapy for which alternate pain management options (including long-acting formulary opioids) have been shown to be inadequate or not tolerated. • BBUP may be a treatment option for patients with significant renal impairment and those with dysphagia/other gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of orally administered immediate-release or ER/LA opioids.

Background

Purposes for review

BBUP was approved by the FDA in October, 2015; it is the second buprenorphine product for management of chronic pain (the other is Butrans).

The purposes of this abbreviated review are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to considering BBUP for addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Also to be determined: Does BBUP have clinical advantages over existing alternatives? What safety issues need to be considered? Does BBUP have specific characteristics best managed by the nonformulary process, prior authorization, criteria for use?

Other therapeutic options

Alternative oral and transdermal opioid alternatives are shown below; see reference 5 for opioid equianalgesic dose ratios.

Formulary Alternatives	Other Considerations
Tramadol tablets	CIV
Hydrocodone/acetaminophen tablets	CII
Oxycodone/acetaminophen tablets	CII
Morphine sulfate sustained action tablets	CII
Hydromorphone immediate-release tablets	CII
Fentanyl transdermal patch	CII, see VA CFU
Buprenorphine transdermal patch (Butrans)	CIII, see VA CFU
Oxycodone liquid	CII
Oxycodone HCL SA tablets	CII, abuse-deterrent formulation; see VA CFU
Oxymorphone HCL SA tablets	CII, abuse-deterrent formulation; see

	VA CFU
Methadone HCl tablets	CII, see VA Recommendations for Use
Tapentadol ER tablets (Nucynta ER)	CII, see VA CFU
Nonformulary Alternatives	**Other Considerations**
Morphine sulfate ER capsules (Kadian, Avinza)	CII
Morphine sulfate and naltrexone HCL ER capsules (Embeda)	CII, abuse-deterrent formulation
Hydromorphone HCL ER tablets (Exalgo)	CII, abuse-deterrent formulation
Levorphanol	CII

Efficacy (FDA-approved Indications) [2-4]

Literature Search Summary

A literature search was performed on PubMed/Medline (to July 2016) using multiple search terms and combinations of terms including buccal buprenorphine and Belbuca. www.ClinicalTrials.gov was utilized to identify unpublished trials with or without results. Reference lists of articles were searched for relevant general information.

FDA approval of BBUP was based on three 12-week double-blind, placebo-controlled clinical trials in patients with moderate-to-severe low back pain. One study (BUP 301, NCT01256450) performed using lower strengths of buprenorphine buccal film (60, 120, 180, or 240 mcg) did not show a statistically significant pain reduction for BBUP compared to placebo. Studies in opioid-naïve patients (BUP 308, NCT01633944) given 75, 150, 300, or 450 mcg or in opioid-experienced patients (BUP 307, NCT01675167) given 150, 300, 450, 750, or 900 mcg are detailed in this review.

Quality of Evidence

The overall GRADE quality of evidence for efficacy was high. All of the published trials were sponsored by the drug manufacturer.

Review of Efficacy [2-4]

Efficacy and Tolerability of BBUP in opioid-naïve patients with moderate to severe chronic low back pain (CLBP) [BUP 308, NCT 01633944] [2]

- BUP 308 was a multicenter, double-blind, placebo-controlled, enriched enrollment, randomized – withdrawal study conducted for the purpose of determining analgesic efficacy of BBUP every 12 hours in opioid naïve patients with moderate to severe CLBP.

Study design

- Key eligibility requirements for enrollment: opioid-naïve adults ≥ 18 years of age with CLBP as their primary pain source for ≥ 6months. CLBP could include pain of neuropathic or non-neuropathic origin, or pain after LBP surgery, but not pain due to other chronic conditions (cancer, arthritis, postherpetic or diabetic neuropathies, fibromyalgia, neural compression or meningitis).
- Patients with clinically significant sleep apnea, unstable cardiac disease, personal or family history of long QT Syndrome were excluded from the study.
- The study included a 2-week screening period, an up to 8 week open-label titration phase, a 12 week double-blind treatment phase, and a final 2 week follow-up phase.
- To progress to the open-label titration phase, patients had to:
    - be stable on an analgesic regimen for at least 4 weeks; the regimen could include non-opioid agent(s) and also permitted opioids at a dose ≤ 10mg morphine equivalent dose day (MEDD).

  - score ≥ 10 at screening on the Roland Morris Disability Questionnaire (RMDQ) [scores range from 0 (no disability) to 24 (maximum disability)] and
  - have a mean average daily pain intensity score ≥ 5 to < 10 [on 11 point numeric rating scale (NRS)]
- All prior analgesic medications were discontinued at the start of the open-label titration phase. BBUP titration began at 75 mcg once daily, progressed to 75 mcg twice daily, then to 150, 300, or 450 mcg twice daily. Patients were titrated to a dose of BBUP that provided well-tolerated analgesia ≤ 4 NRS for the last 14 days of the open-label phase.
- Patients with a mean average pain intensity ≤ 4 NRS for the last 3 days before randomization and ≥ 2 points lower than the score at screening were eligible for randomization.
- To be eligible for the double-blind treatment phase, patients had to have been titrated to a BBUP dose ≥ 150 mcg BID, had to have received their optimal dose for ≥2 weeks, and had to have taken ≤ 1 dose/day of acetaminophen during the last 7 days.
- Patients were randomized 1:1 to receive BBUP twice daily at optimal dose determined during open-label phase or placebo
- Investigator follow-up occurred weekly for first 2 weeks, then every 2 weeks to week 12 or the end of treatment. All patients were provided with hydrocodone 5mg/acetaminophen 325mg (H/APAP) for rescue analgesia for the initial 2 weeks; thereafter, acetaminophen 500 or 1000 mg was available. Patients who required > 2 tablets/day of H/APAP during the first 2 weeks or > 1000 mg/day of acetaminophen after the first 2 weeks were withdrawn from the study.
- Following week 12 or the end of treatment was a 2 week follow-up phase during which the study treatment was discontinued; patients were either converted to an alternate analgesic regimen or offered enrollment in a long-term, open-label safety study.
- The primary efficacy endpoint was change in mean NRS average pain intensity score from baseline to week 12.
- Secondary efficacy endpoints included:
  - Proportion of patients with ≥ 30% reduction or a ≥ 50% reduction in NRS score
  - Use of patient-reported non-opioid and opioid rescue medications
  - Scores on patient-reported outcome measures: Patient Global Impression of Change [PGIC, rated from 0 (no change) to 7 (a great deal better)], RMDQ and the Medical Outcomes Score Sleep Subscale (MOS).
- Adverse events (AEs) were documented; a determination was made for each regarding intensity and relationship to study treatment.

Results

- Of the 752 patients that entered the open-label phase; 462 were randomized to receive BBUP (n = 229) or placebo (n = 232). Two hundred ninety patients were not randomized – 109 withdrew from BBUP treatment due to an AE and 33 withdrew due to inefficacy. A total of 420 patients were included in the intent to treat (ITT) population; 41 patients were excluded due to inadequate data quality at one site.
- Patient characteristics were similar between patients randomized to BBUP or placebo; the majority of patients assigned to double-blind treatment were white (71%), female (56%), with a mean age of 50 years and mean BMI > 30 kg/m^2.
- Before open-label titration, patients had a mean ± SD NRS pain score of 7.22 ± 1.09, signifying moderate to severe pain. At randomization the BBUP and placebo groups had respective scores of 2.85 ± 1.00 and 2.81 ± 1.12, both representative of good pain control.
- At week 12, for the primary endpoint, a significantly higher increase in NRS pain intensity score from baseline occurred in patients receiving placebo compared to those on active treatment with BBUP (1.59 ± 2.04 *versus* 094 ± 1.85, p = 0.0012).
- For the secondary endpoints:
  - A significantly greater proportion of patients treated with BBUP had a ≥ 30% reduction in pain compared to placebo (p = 0.0012); however, the proportion of those with ≥ 50% reduction in pain was not different between the BBUP and placebo groups.
  - Patient-reported use of rescue medication results were mixed; significantly fewer BBUP patients used rescue medications than did placebo patients, but only at weeks 2,3,6,8, and 10 (p < 0.05).

  - PGIC scores were lower at week 12 in patients on placebo (3.9 ± 1.99) *versus* those randomized to BBUP (4.5 ±1.75) [p = 0.0011]. RMDQ and MOS values were not significantly different between treatment groups at 12 weeks.
- Seventy-two percent of patients (540 of 749) reported at least one AE during the open-label titration phase; AE were representative of those known to occur with buprenorphine including nausea (47.3%), constipation (12.4%), somnolence (6.8%), vomiting (6.1%) and dizziness (5.7%). In the double-blind treatment phase, the percentage of patients reporting any AE was similar between patients receiving BBUP or placebo (41.0% *versus* 43.5%, respectively). There were no cases of respiratory depression reported in either phase of the study. Serious AEs occurred in 3 patients in the BBUP group during the double-blind treatment phase but were not deemed related to study treatment.

Efficacy and Tolerability of BBUP in opioid-experienced patients with moderate to severe chronic low back pain (CLBP) [BUP 307, NCT01675167] [3]

- Like BUP 308, BUP 307 was a multicenter, double-blind, placebo-controlled, enriched enrollment, randomized-withdrawal study, but was conducted to determine the analgesic efficacy of BBUP every 12 hours in opioid-experienced patients with moderate to severe CLBP.

Study design

- Eligibility requirements and exclusion criteria for BUP 307 were essentially the same as previously detailed for BUP 308 with the exception that enrollees entered the study on an opioid morphine equivalent daily dose (MEDD) of 30 to 160 mg (including stable daily maintenance dose and any additional as-needed rescue opioid).
- Patients recorded all analgesic medication use and completed a daily NRS pain assessment during the 2 week screening phase.
- Following the screening phase, there was an up to 4 week opioid taper phase. Opioid doses were tapered to ≤ 30 mg MEDD; patients were required to report mean average daily pain intensity scores of ≥ 5 for 3 consecutive days during the screening or opioid taper before entering the open-label titration with BBUP. Once this level of pain intensity was reached, patients were permitted to use H/APAP 5 mg/325 mg as needed every 6 hours up to maximum of 4 tablets/day as analgesic rescue.
- Patients entering the open-label titration phase began treatment with BBUP 150 or 300 mcg every 12 hours depending upon the opioid dose at the end of the screening phase. BBUP doses were increased every 4 to 8 days until patients achieved a 3-day mean pain score ≤ 4 or reached a dose of 900 mcg every 12 hours. Patient responders were defined as those who tolerated the open-label titration well and achieved NRS pain scores ≤ 4 for 14 days on BBUP with no more than 1 dose/day of H/APAP. Responders were eligible for randomization if their mean pain-intensity score was ≤ 4 and at least 2 NRS points less than their pain score either at the end of the opioid taper or at screening.
- Patients were stratified within their BBUP dose and randomized 1:1 to receive BBUP or placebo every 12 hours for 12 weeks. To minimize risk of opioid withdrawal in placebo-randomized patients, up to 2 doses/day of opioid rescue (1-2 tabs H/APAP) were allowed to all patients for the first 2 weeks and up to 1 dose/day thereafter. Patients who required > 1 dose/day on > 2 occasions were withdrawn from the study. Patients who experienced moderate opioid withdrawal within 2 weeks of randomization were also withdrawn from the study.
- Primary and secondary efficacy endpoints were as described for BUP 308. Patient responders were defined as the cumulative proportion of patients who completed the 12-week double-blind phase and achieved pain reductions ≥ 30% and ≥ 50% from the start of the open label titration phase to week 12 of the double-blind treatment phase.

Results

- Eight-hundred fifteen patients entered the open-label phase; 511 were randomized to receive BBUP (n = 254) or placebo (n = 257). Demographic characteristics were well-balanced both for the patients in the open-label phase and among patients that were randomized. Compliance was high throughout the study. The two most frequent causes of discontinuation during the open-label phase included AEs (9.9%) and lack of efficacy (7.7%).
- Of the patients who received BBUP, 87.0% had been on previous opioid therapy <80 mg MEDD, 10.2% on 80 to 120 mg MEDD, and 2.8% had been on >120 mg MEDD. At the end of titration, the

distribution of BBUP doses (every 12 hours) among patients randomized to active treatment was: 150 mcg (4%), 300 mcg (12%), 450 mcg (14%); 600 mcg (17%); 750 mcg (17%), and 900 mcg (36%).
- Discontinuation rates were 18.9% in the BUP group and 23.7% in the placebo group; discontinuations due to lack of efficacy were 7.5% and 23.7% in the BBUP and placebo groups, respectively.
- In the intent-to-treat population, the mean pain score of 6.7 following opioid taper declined to 2.8 after the BBUP titration period; after randomization, the mean pain scores were lower in the BBUP group versus placebo [mean change of -0.98 (95% CI, -1.32 to -0.64; $p < 0.001$)].
- For the secondary measures, compared to placebo at week 12, a larger percentage of BBUP patients had pain reduction ≥ 30% and ≥ 50%. Also, a lower percentage of BBUP patients required rescue medication and mean PGIC score was higher following BBUP (all $p < 0.001$). There was less disability associated with BBUP treatment vs. placebo as determined by RMDQ scores ($p < 0.008$).
- During the mean titration period of 38.7 days, 60% of patients experienced on or more AEs and 10.2% discontinued BBUP because of AEs. During the double-blind period AEs were reported by 48% of patients; 5.1% discontinued because of this but more discontinuations occurred in the placebo group than the BBUP group (8.2 versus 2.0%). The most common AEs during the titration phase were those typically associated with opioids. There were no reports of respiratory depression and no deaths.

Webster et al. (2016) performed a randomized, double-blind, double-dummy, active-controlled two period crossover study to evaluate the tolerability of switching patients on chronic μ-opioid agonist therapy (80 to 220 mg MEDD) to a reduced dose of BBUP without taper.[4] A conversion ratio of 100:1 for morphine to buprenorphine was used for the study. Thirty-nine patients with chronic pain ≥ 6 months were randomized; 33 were assigned to group I and were taking 80-160 mg MEDD, and 6 were assigned to dose group II that were taking 161-220 mg MEDD. Each subject was randomized to one of two treatment sequences (AB or BA). Treatment A was two doses of BBUP (300 mcg for group I patients and 450 mcg for group II patients); treatment B was 2 doses of their original μ-agonist (morphine or oxycodone) reduced by 50%. The primary endpoint was proportion of patients with a maximum Clinical Opiate Withdrawal Scale (COWS) score ≥ 13 (indicating moderate withdrawal) or use of rescue medication for withdrawal symptom management during the 24-hour study period. Upon study completion, only 2 of the group I patients met the study definition for opioid withdrawal (one experienced withdrawal with both treatments A and B, the other with treatment B only). None of the group II patients met the definition for withdrawal. The authors concluded that switching patients to a 50% MEDD dose of BBUP has comparable safety and tolerability to reducing a patient to a 50% MEDD of their current full μ-agonist agent. Study limitations included uncertainty regarding exactness of the μ-agonist to buprenorphine conversion ratio, and the limited number of full μ-agonists trialed. Conversion from a full μ-agonist at 80-160 MEDD to BBUP 300 mcg every 12 hours is consistent with recommendations in product labeling (see Table 3, page 11).

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

There is potential use of BBUP in the management of pain *not severe enough* to require daily, around-the-clock, long-term opioid treatment and/or for which alternative treatment options *have not yet* been trialed or shown to be inadequate.

There are 9 trials of BBUP listed at www.clinicaltrials.gov (accessed July 29, 2016). One completed study (NCT00941304) was a double-blind, double-dummy, placebo and active controlled efficacy, safety and tolerability study of BBUP in the treatment of acute dental pain (third molar extraction); numerous pain outcome measures trended towards improved results with 50 mcg BBUP compared to oxycodone 5mg.

Safety [1]

(For more detailed information, refer to the product information.)

	Comments
Boxed Warning	• BBUP exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor for development of these behaviors or conditions. • Serious, life-threatening or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients on proper administration of BBUP to reduce the risk. • Accidental exposure to BBUP, especially in children, can result in fatal overdose of buprenorphine. • Prolonged use of BBUP during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
Contraindications	• Significant respiratory depression • Acute or severe bronchial asthma • Known or suspected gastrointestinal obstruction, including paralytic ileus • Hypersensitivity to buprenorphine
Warnings/Precautions	• *Risk of life-threatening respiratory depression in elderly, cachectic, debilitated patients, and those with chronic pulmonary disease:* monitor closely. • *Risk of prolonged QTc interval:* avoid in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic drugs. • *Severe hypotension:* monitor for hypotensive effects during dose initiation and titration. • *Risk of use in patients with increased intracranial pressure, brain tumors, head injury or impaired consciousness:* monitor for sedation and respiratory depression.

Safety Considerations [1-4]

- A total of 2,127 patients were treated with BBUP during controlled and open-label clinical trials in patients with chronic moderate to severe pain, with 504 patients treated for approximately 6 months and 253 patients treated for approximately 1 year. See *Review of Efficacy* and *Adverse Reactions* for summaries of adverse reaction reports from BBUP clinical trials.
- BBUP contains buprenorphine HCl, a schedule III controlled substance with abuse, misuse, addiction and criminal diversion potential similar to other schedule III opioids. Proper patient assessment, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and storage are measures which can help to reduce abuse of opioids.
- Buprenorphine produces μ-opioid receptor-mediated respiratory depression by direct action on brainstem respiratory centers; however, unlike other opioids, buprenorphine exhibits a dose-ceiling effect.
- Abuse of BBUP poses a risk of overdose and death. Abuse may occur when BBUP is used in the absence of legitimate purpose, or by swallowing, snorting, or injecting buprenorphine extracted from the film product. Risk for overdose or death can be increased when BBUP is used or abused in combination with alcohol or other CNS depressant substances such as sedatives, hypnotics, neuroleptics or other opioids.
- Risk for overdose death can be decreased with provision of naloxone rescue and exercise of other risk

mitigation strategies. Higher doses of naloxone and a longer time to onset of mu-receptor antagonist effects (e.g., 1–3 hours) may be required to reverse respiratory depression caused by buprenorphine overdose than are required most other μ-opioid agonists. Duration of naloxone reversal of respiratory depression is less than the duration of buprenorphine, thus requiring continued patient monitoring and likely need for supplemental dose(s) of naloxone.

- Both tolerance and physical dependence can develop during BBUP therapy; BBUP should not be abruptly discontinued in physically dependent patients due to risk for withdrawal syndrome. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit difficulties and withdrawal symptoms.
- Patients on long-term BBUP therapy who require acute or perioperative pain management (for elective or emergency surgery) should be managed by anesthesiologists and other experts familiar with managing patients who are physically dependent on opioids. These patients may require high doses and prolonged opioid therapy because of opioid tolerance and may experience opioid withdrawal symptoms if inadequately dosed on perioperative opioids.
- QTc prolongation with BBUP has been observed; of the 1590 patients treated with BBUP in controlled and open-label chronic pain trials at doses up to 900 mcg every 12 hours, 2% demonstrated a prolongation of rate-corrected QTc to a post-baseline value between 450-480 msec during therapy.
- Buprenorphine reduces gastrointestinal secretions and motility, increases smooth muscle tone, slows digestion, and thereby causes constipation.
- BBUP and other opioid-containing medications should be stored safely and out of sight and reach of children.
- BBUP is covered under the Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (ER/LA Opioid Analgesics REMS)
  [see http://www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_opioid_2016-04-26_REMS_full.pdf and http://www.er-la-opioidrems.com/IwgUI/rems/products.action]

Adverse Reactions [1]

Common adverse reactions	*Incidence ≥ 5%:* nausea, headache, dizziness, constipation, somnolence, vomiting, dry mouth, fatigue, and diarrhea
Death / Serious adverse reactions	The most common serious adverse reactions reported in clinical trials with BBUP (all ≤ 0.2%): cellulitis, pneumonia, ileus, atrial fibrillation, coronary artery disease, cerebrovascular accident, syncope, transient ischemic attack, chest pain, non-cardiac chest pain, ankle fracture, cholecystitis, osteoarthritis and dehydration.
Discontinuations due to adverse reactions	The most common adverse events (≥ 2%) leading to discontinuation of BBUP in clinical trials were nausea, vomiting, and liver function test abnormalities.
Other notable adverse reactions	*Incidence ≥ 1% to < 5%:* drug withdrawal syndrome, falls

Drug-Drug Interactions [1]

Refer to product information for additional details.

- *Benzodiazepines*: alter usual ceiling effect on buprenorphine-induced respiratory depression (monitor; warn patients)
- *CNS Depressants (including Alcohol)*: increase risk of hypotension, respiratory depression, profound sedation, coma and death (monitor; consider dose reduction of one or both agents)
- *CYP3A4 Inhibitors*: decrease buprenorphine clearance, increase plasma drug concentrations and increase or prolong opioid effect (monitor for respiratory depression and sedation; consider dose adjustments)
- *CYP3A4 Inducers*: addition can increase buprenorphine clearance, decrease plasma drug concentrations and decrease opioid effect or, in patients physically dependent on buprenorphine, cause abstinence / withdrawal syndrome (monitor for withdrawal; consider dose adjustments). Discontinuation of CYP3A4 inducers may cause increase in plasma buprenorphine concentrations and

result in respiratory depression (monitor for respiratory depression and sedation; consider dose adjustments)
- *Muscle Relaxants*: buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and increase degree of respiratory depression (monitor)
- *Anticholinergics*: increased risk of urinary retention and / or severe constipation, which may lead to paralytic ileus (monitor)

Risk Evaluation

As of 11August 2016.

Sentinel event advisories

- **High alert medication:** The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes (opioids) which have a heightened risk of causing significant patient harm when used in error.
- None specific for BBUP or buprenorphine. The Institute for Safe Medication Practices has issued sentinel event advisories on the fentanyl transdermal system.

Look-alike/sound-alike error potential

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Buprenorphine buccal film 75, 150, 300, 450, 600, 750 and 900 mcg	None	None	None	Buprenorphine HCl (BUPRENEX) Buprenorphine-naloxone BUPROBAN Bupropion Buspirone Butorphanol
Belbuca	None	None	None	Belsomra Belviq

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Pharmacokinetics [1, 6, 7]

BBUP is manufactured with BioErodible MucoAdhesive (BEMA) delivery technology composed of flexible, water-soluble polymeric films that adhere to the moist buccal mucosa and then erode over a period of minutes. The bilayer BEMA delivery system facilitates transmucosal delivery by increasing adhesion and residence time (which potentiates buprenorphine permeation and absorption) and minimizing the amount of buprenorphine dissolved in the saliva and swallowed. The backing layer which assures the unidirectional delivery of buprenorphine is comprised of hydroxypropyl and hydroxyethyl cellulose; the active drug layer contains polycarbophil and carboxymethylcellulose sodium.

The transmucosal buprenorphine dose delivered by BBUP is determined by the film size (surface area) and buprenorphine concentration in the formulation. A pharmacokinetic evaluation by Bai et al. (2016) indicated that systemic plasma levels of buprenorphine increase in a linear manner proportional to the single dose administered over a range of 75 to 1200 mcg (Table 1).

Table 1: Single dose mean ± SD BBUP pharmacokinetic parameters.

Regimen	Dosage (mcg)	C_{max} (ng/mL)	AUC $_{0-t}$ (h·ng/mL)	AUC $_{0-\infty}$(h·ng/mL)	T_{max} * (h)
Single Dose	75	0.17±0.30	0.46±0.22	0.63±0.24	3.00 (1.50-4.00)
	300	0.47±0.47	2.00±0.68	2.3±0.68	2.50 (0.50-4.00)
	1200	1.43±0.45	9.6±2.9	10.5±3.32	3.00 (1.00-4.00)

* Tmax values reported as median and range

A linear relationship was also shown for Cmax, AUC $_{0\text{-}t}$ and AUC $_{0\text{-}\infty}$ following multiple twice daily dosing with film strengths of 60, 120, 180 and 240 mcg .[6]

Ingestion of liquids (hot, cold, or at room temperature) during BBUP administration reduces systemic exposure to buprenorphine 23 to 27%; co-administration of acidic liquids (for example, decaffeinated cola) decreased buprenorphine exposure by approximately 37%.

Table 2: Selected Pharmacokinetic Properties of BBUP

Parameter	Value
Mean absolute bioavailability (relative to IV)	46% to 51%*
T max (following single-dose)	2.5 to 3 hours
Mean plasma elimination half-life	27.6 hours
Time to steady state (days)	~ 3 days (with every 12 hour dosing)
Metabolism	Substrate of CYP3A4 which mediates N-dealkylation to norbuprenorphine (active). The parent compound and norbuprenorphine are also subject to glucuronidation.
Elimination	69-70% fecal, mostly unchanged; 27-30% renal, mostly changed
Dialyzable	No

* Calculated at doses of 75, 300 and 1200 mcg

Dosing and Administration [1]

- Refer to the product information for full dosing information.
- BBUP should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.
- Before initiation of BBUP, patients should be counseled regarding the potential risks and benefits of opioid therapy, proper administration technique, disposal instructions, and monitoring requirements.
- Initiation and titration of BBUP should be approached for each patient individually, taking into account the patient's level of pain, prior opioid analgesic experience, and risk factors for addiction, misuse, and abuse.
- Patients should be monitored closely for respiratory depression, particularly within the initial 24-72 hours of initiation of therapy and following dosage increases.
- BBUP doses of 600 mcg, 750 mcg, and 900 mcg should be used only following titration from lower doses of BBUP.

Initial Dosing

- *Use of BBUP as the First Opioid Analgesic (Opioid Naïve Patients)*
  - BBUP treatment should be initiated with a 75 mcg film once daily (or, if tolerated, every 12 hours for at least 4 days); then increase the dose to 150 mcg every 12 hours.
  - Thereafter, individual titration can proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days, until adequate analgesia is achieved with acceptable tolerance.

- *Conversion from Other Opioids to BBUP*
  - There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids.
  - To reduce the risk of opioid withdrawal, the dose of other opioid should be tapered to no more than 30 mg oral morphine equivalent daily dose (MEDD) before initiating therapy with BBUP
  - Following the opioid taper, initiate BBUP based upon the patient's opioid MEDD prior to taper, as detailed in Table 3.

- Thereafter, individual titration can proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days, until adequate analgesia is achieved with acceptable tolerance
- Patients may require supplemental immediate-release opioid analgesics during the opioid taper period and during titration.
- BBUP may not provide adequate analgesia for patients requiring > 160 mg MEDD; in these instances, consider an alternative analgesic.
- Conversion from Methadone to BBUP: Close monitoring is of particular importance; the ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure.

Table 3: Initial BBUP dosing based upon prior opioid MEDD [1]

Prior Daily Dose of Opioid Before Taper to 30mg oral MEDD	Initial BBUP Dose
< 30mg oral MEDD	75 mcg once daily or every 12 hours
30 to 89 mg oral MEDD	150 mcg every 12 hours
90 to 160 mg oral MEDD	300 mcg every 12 hours
> 160 mg oral MEDD	Consider alternative analgesic

Titration and Maintenance of Therapy

- The titration interval of 4 days is based upon the pharmacokinetic profile of BBUP and time to reach steady-state plasma levels (see *Pharmacokinetics*, pages 9-10).
- **The maximum BBUP dose is 900 mcg every 12 hours; this maximum dose should not be exceeded because of the risk of QTc interval prolongation.**
- Patients should be continually re-evaluated to assess level of pain control, occurrence of adverse effects, and to monitor for development of addiction, misuse, or abuse.
- There should be periodic assessment during long term therapy to determine the continued need for treatment with an opioid analgesic.

Discontinuation of BBUP Therapy

- BBUP should not be abruptly discontinued; the dose should be gradually titrated downward to prevent signs and symptoms of withdrawal in the physically dependent patient. During this period the use of an appropriate immediate-release opioid medication should be considered.

BBUP Dosage Adjustments in Special Populations

- See next section *Special Populations (Adults)*

BBUP Administration

- The patient should wet the inside of the cheek or rinse the mouth with water to wet the area for placement of the buccal film
- BBUP should then be applied immediately against the inside of the cheek, yellow side down.
- The BBUP film should be held in place with clean, dry fingers for 5 seconds, then left in place on the inside of the cheek until fully dissolved
- Properly applied, BBUP adheres to the moist buccal mucosa and will completely dissolve within approximately 30 minutes.
- The BBUP film should not be manipulated with the tongue or fingers; eating food or drinking liquids should be avoided until the film is dissolved. BBUP film, if chewed or swallowed, may result in lower peak buprenorphine concentrations and lower bioavailability than when used as directed (see *Pharmacokinetics*, pages 9-10).

Disposal

- Patients should dispose of BBUP film when it is no longer needed.
- The FDA-labeling for BBUP recommends that unused product may be disposed of by removing product from the foil packaging and flushing product down the toilet, followed by discarding empty foil packaging in trash.

Special Populations (Adults)

Elderly	• Of the 2,127 patients in controlled and open-label chronic pain trials of BBUP, 340 patients were 65 years or older. • The incidences of selected BBUP-related adverse effects were higher in older subjects. • No notable differences in pharmacokinetics of BBUP were observed from population pharmacokinetic analysis in subjects aged 65 compared to younger subjects. • In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, taking into account the frequency of reduced hepatic, renal or cardiac function and increased incidence of concomitant disease or other drug therapy.
Pregnancy	• Pregnancy Category C • Prolonged use of opioids during pregnancy may result in physical dependence in the neonate and result in neonatal opioid withdrawal syndrome shortly after birth. • Opioids cross the placenta and may cause respiratory depression in neonates. • Opioids can prolong labor, although this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.
Lactation	• There are no data on the effects of BBUP on milk production. • Buprenorphine and its metabolite norbuprenorphine are excreted in breast milk and in the urine of breastfed infants. • Excess sedation and respiratory depression can occur in a breastfed infant and opioid withdrawal symptoms can occur in infants when mothers discontinue buprenorphine therapy or when breastfeeding is stopped. • Due to the potential for serious adverse reactions, breastfeeding is not recommended during treatment with BBUP.
Renal Impairment	• No differences in buprenorphine pharmacokinetics were seen when buprenorphine 0.3 mg was administered intravenously to 9 dialysis-dependent patients and 6 patients with normal renal function.
Hepatic Impairment	• BBUP has not been evaluated in patients with severe hepatic impairment. • Buprenorphine plasma levels were higher and its half-life was found to be longer in subjects with moderate and severe hepatic impairment dosed with buprenorphine sublingual tablets. • Patients with moderate or severe hepatic impairment should be closely monitored when administered BBUP; those with severe hepatic impairment (i.e., Child-Pugh C) should have their starting and titration doses reduced by half that of patients with normal liver function (from 150 mcg to 75 mcg).
Oral mucositis	• Patients with known or suspected mucositis should have their start dose or titration incremental dose reduced by half (compared to patients without mucositis), as buprenorphine may be absorbed more rapidly from BBUP resulting in higher Cmax (~79%) and AUC (~56%) compared to healthy age- and gender matched controls.
Pharmacogenetics/genomics	• Genetic factors likely influence response to buprenorphine: polymorphisms of the gene encoding the delta-opioid receptor (OPRD1) have been noted to influence outcomes related to opioid use disorder and pain perception.[8, 9]

Projected Place in Therapy [1-5]

- Consideration of long term opioid therapy (LTOT) is most appropriately reserved for patients who have intractable chronic pain that cannot be adequately managed with more conservative or interventional methods. LTOT should be prescribed only after thorough patient evaluation, weighing of realistic potential

benefits with known risks, and establishment of a patient-specific treatment plan including goals for both pain and function and patient and clinician responsibilities for managing and monitoring therapy.[5]

- There are 2 randomized, placebo-controlled trials of good quality that document the 12 week efficacy of twice-daily BBUP in the relief of moderate to severe chronic low back pain in opioid naïve and opioid experienced patients. There is an additional RCT indicating that patients with chronic pain may be converted, without taper, but with comparable safety and efficacy, from long term morphine or oxycodone (80 to 160 MEDD) to an estimated 50% MEDD dose of BBUP.
- The most common adverse events associated with BBUP are those known to occur with the use of opioid analgesics. QT prolongation has been reported with recommended doses of BBUP; the maximum dose of BBUP is set at 900 mcg every 12 hours due to the added risk of QTc interval prolongation with higher doses.
- Buprenorphine produces μ-opioid receptor-mediated respiratory depression; but, unlike pure μ-opioid agonists, there is a dose-ceiling for this effect. Respiratory depression was not reported in the published studies of BBUP; however, abuse or misuse of BBUP may still pose a risk of overdose and death.
- Benzodiazepines and other CNS depressants (including alcohol, sedative/hypnotics, neuroleptics, and other opioids) can alter the usual ceiling effect of buprenorphine-induced respiratory depression and magnify other CNS-mediated effects.
- Buprenorphine undergoes extensive metabolism through the CYP3A4 system requiring attention to the potential for significant drug interactions with other medications that are substrates, inhibitors, or inducers of this system.
- While the CIII status of BBUP infers a reduced potential for abuse relative to CII opioids, little is known about the potential for abuse by snorting or injecting buprenorphine extracted from buccal film.
- Potential place in therapy: BBUP may be a consideration in the management of moderate to severe chronic pain that requires round-the-clock LTOT for which alternate pain management options (including long-acting formulary opioids) have been shown to be inadequate or not tolerated. BBUP may be a treatment option for patients with significant renal impairment and those with dysphagia/other gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of orally administered immediate-release or ER/LA opioids.

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Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.